

THE AMENDMENTS

Formalities:

Please change the Attorney Docket No. to "320185.00104."

In The Specification:

A marked-up version of the specification showing the amendments is attached hereto as Exhibit A. Matter that has been deleted from the specification is indicated by brackets and matter that has been added is indicated by underlining.

Please amend the specification as follows:

Please replace the paragraph beginning at page 9, line 3, and ending at page 13, line 24, with:

It is to be understood that the present invention is not limited to the examples described herein, and other serine protease inhibitors known in the art are used within the limitations of the invention. For example, one skilled in the art can easily adopt inhibitors as described in WO 98/24806, which discloses substituted oxadiazole, thiadiazole, and triazole as serine protease inhibitors. U.S. Pat. No. 5,874,585 discloses substituted heterocyclic compounds useful as inhibitors of serine proteases, including: (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(methyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(difluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2,6-difluorobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trans-styryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trans-4-trifluoromethylstyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trans-4-methoxystyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-thienylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(phenyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; and (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylpropyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide. U.S. Patent No. 5,216,022 teaches other small molecules useful for the practice of this invention, including: (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide (also known as CE-2072); (benzyloxycarbonyl)-L-valyl-N-[1-(2-(3-(methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(methyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-trifluoromethylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(4-dimethylamino benzyl)-1,3,4-oxadiazolyl)carbonyl)-

2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(1-naphthylenyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-ditrifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(biphenylmethine)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-phenylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(cyclohexylmethylene)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethyldimethylmethylene)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(1-naphthylmethylene)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-pyridylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-diphenylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide; 2-(5-

61 [(benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-(S)-2-methylpropyl]acetamide; 2-(5-amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 2-[5-[(benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-(S)-2-methylpropyl]acetamide; 2-[5-amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-methylpropyl]acetamide; (pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide; (pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)(1,2,4-oxadiazolyl)-(S)-methylpropyl]amide; (2S,5S)-5-amino-1,2,4,5,6,7-hexahydroazepino-[3,2,1]-indole-4-one-carbonyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-(R,S)-2-methylpropyl]amide; BTD-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide; (R,S)-3-amino-2-oxo-5-phenyl-1,4-benzodiazepine-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; (benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide; (benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide; acetyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide; 3-(S)-(benzyloxycarbonyl)amino)-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 3-(S)-(amino)-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide trifluoroacetic acid salt; 3-(S)-[(4-morpholinocarbonyl-butanoyl)amino]-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-

1,3,4-oxadiazolyl)carbonyl)-2-(R,S)-methylpropyl]acetamide; 6-[4-fluorophenyl]-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl(hydroxymethyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-benzyl-4-oxothiazolidin-3-yl)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 2-(2-(R,S)-benzyl-4-oxothiazolidin-3-yl oxide)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(R,S)-methylpropyl]acetamide; (1-benzoyl-3,8-quinazolidinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; (1-benzoyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; (1-phenyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; (1-phenyl-3,6-piperazinedione)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)]-2-(S)-methylpropyl]acetamide; 3-[(benzyloxycarbonyl)amino]-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 3-[(benzyloxycarbonyl)amino]-7-piperidinyl-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 3-(carbomethoxy-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 3-(amino-quinolin-2-one)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 3-[(4-morpholino)aceto]amino-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 3,4-dihydro-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 1-acetyl-3-(4-fluorobenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 1-acetyl-3-(4-dimethylaminobenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 1-acetyl-3-(4-carbomethoxybenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 1-acetyl-3-[(4-pyridyl)methylene]piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-benzyl-3-(R)-benzyl-piperazine-2,5-dione]-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-benzyl-3-(S)-benzylpiperazine-2,5-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-benzyl-3(R)-benzylpiperazine-2,5-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-benzyl-3-(S)-benzylpiperazine-2,5-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-benzyl-3-(S)-benzylpiperazine-2,5-dione]-N-[1-(3-(5-(2-dimethylaminoethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-methyl-3-(R,S)-phenylpiperazine-2,5-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 4-[methyl-3-(R,S)-phenylpiperazine-2,5-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-(4-morpholinoethyl)-3-(R)-benzylpiperazine-2,5-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R,S)-phenyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R)-benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 5-(S)-benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-